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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/975,813	10/12/2001	Jeffrey A. Miller	DM-6907-A	1068

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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 07/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/975,813	MILLER ET AL.	
	Examiner	Art Unit	
	Christian L. Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *26-30 and 33-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-25,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/12/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S. 07

DETAILED ACTION

Election/Restriction

1. Applicants' election without traverse of Group I, claims 1-25, 31, and 32, in the response dated 07/26/2004 is acknowledged. Affirmation of this election must be made by applicant in replying to this Office action. Claims 26-30 and 33-52 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. Claims 1-25, 31, and 32 are under consideration in this Office Action.

3. The disclosure is objected to because of the following informalities: a copy of the application data sheet indicated on the transmittal paper dated10/12/2001 is missing. Appropriate correction is required by submitting a copy of the said application data sheet for the instant application.

Claim Rejections - 35 U.S.C. § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5 Claims 1-25, 31, and 32 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-25, 31, and 32, as written, do not sufficiently distinguish over peptides as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated peptide" or "purified peptide". See MPEP 2105.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 15-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 15 and 16, the phrase "product peptide" renders the claims vague and indefinite. The meaning of the phrase is unclear since it is not certain if applicants intended the claims to encompass a proteolytically cleaved peptide fragment. Claims 17-23 which depend from claims 15 or 16 are also rejected because they do not correct the defect of claims 15 and 16.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-25, 31, and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are genus claims encompassing several different genera. Genus claim 1 is directed toward any peptide of any function, amino acid sequence, and structure having any ADMP-susceptible cleavage site of any amino acid sequence and structure. Genus claim 3 is directed toward any peptide of any function, amino acid sequence, and structure comprising amino acids 1-40 of SEQ ID NO: 1. Genus claim 4 is directed toward any peptide of any function, amino acid sequence, and structure comprising an amino acid sequence that is 80% identical to amino acids 1-40 of SEQ ID NO: 1. Genus claim 5 is directed toward any peptide of any function, amino acid sequence, and structure comprising amino acids 1-40 of SEQ ID NO: 2. Genus claim 6 is directed toward any peptide of any function, amino acid sequence, and structure comprising amino acids 1-40 of SEQ ID NO: 3. Genus claim 7 is directed toward any peptide of any function, amino acid sequence, and structure comprising an amino acid sequence that is 80% identical to amino acids 1-40 of SEQ ID NO: 3. Genus claim 15 is directed toward any proteolytically cleaved peptide fragment of any function, amino acid sequence, and structure comprising any amino acid from the N-terminus through P1 of any ADMP-susceptible cleavage site of any amino acid sequence and structure. Genus claim 16 is directed toward any proteolytically cleaved peptide fragment of any function, amino acid sequence, and structure

comprising any amino acid from the P1' of any ADMP-susceptible cleavage site of any amino acid sequence and structure through the C-terminus.

The scope of each genus includes many peptides with widely differing functionally, structural, chemical, and physical characteristics. Furthermore, each genus is highly variable because a significant number of structural differences between genus members exists.

The specification only discloses peptides consisting of SEQ ID Nos: 1, 2, or 3. However, the specification does not disclose additional representative species encompassed by each genus. Furthermore, the specification does not disclose any amino acid sequence and structure that is common to the members of each claimed genus.

In view of the above considerations, one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by members of each claimed genus. Dependent claims 2, 8-14, 17-25, 31, and 32 are also rejected because they do not correct the defects of claims 1, 3-7, 15, and 16.

10. Claims 4, 7, and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated peptide consisting of the amino acid sequence of SEQ ID NO:1 or SEQ ID NO: 3, does not reasonably provide enablement for any peptide of any function, amino acid sequence, and structure comprising an amino acid sequence that is 80% identical to amino acids 1-40 of SEQ ID NO: 1 or SEQ ID NO: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized In re Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claims encompass any peptide of any function, amino acid sequence, and structure comprising an amino acid sequence that is 80% identical to amino acids 1-40 of SEQ ID NO: 1 or SEQ ID NO: 3. The specification provides guidance and examples for making a peptide consisting of the amino acid sequence of SEQ ID NO:1 or SEQ ID NO: 3. However, knowledge regarding the biological utility of the claimed peptides and the specific amino acid residues to change without affecting biological activity of the claimed peptides is lacking.

The amount of experimentation to determine the biological activity the specific amino acid residues to change without affecting biological activity of the claimed peptides is enormous and undue. Such experimentation entails searching and screening for a biological activity of the peptide and screening and searching for any amino acid in SEQ ID NO: 1 or 3 to change (amino acid insertion, deletion, addition, substitution, or combinations thereof) that does not affect biological activity in order to make an amino acid sequence that is 80% identical to SEQ ID NO:

1 or 3. General teaching regarding screening and searching for the claimed invention is not guidance for making the claimed invention. Thus, the amount of experimentation to determine the specific biological function of the claimed peptides as well as their biological utility is undue. Dependent claim 8 is also rejected because it does not correct the defect of claim 4 or 7.

Claim Rejections - 35 U.S.C. § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Fosang et al. (FEBS Lett. 1996 Feb 12;380(1-2):17-20; and GenBank Accession NP_037359 and NP_001126).

Fosang et al. teach the aggrecan G1-G2 peptide substrate which was cleaved by collagenase (MMP-13) into peptide products (85 kDa, 75 kDa, and 50 kDa) at a position corresponding to the VKP_{384}|VFE site of aggrecan (see entire publication especially pp. 19, section *3.3 Digestion of G1-G2 with MMP-13* to section *3.4 N-terminal sequence analysis of an MMP-13 digestion product*). Furthermore, the attached reports for GenBank Accession NP_037359 and NP_001126 show the amino acid sequence of the said peptide substrate.

Thus, the reference teaching anticipates claim 1 since the aggrecan G1-G2 peptide was cleaved by MMP-13 (deemed to be aggrecan degrading metalloprotease (ADMP) because it is a metalloprotease that cleaved the said aggrecan G1-G2substrate); and the said aggrecan G1-G2 substrate contains the ADMP-susceptible cleavage site at a position corresponding to the VKP_{384}|VFE site of aggrecan.

Since the said aggrecan G1-G2 substrate was cleaved at the position corresponding to the VKP_{384}|VFE site of aggrecan, then the one of the cleaved peptide products would inherently have amino acids from the N-terminus through P1 of the ADMP-susceptible cleavage bond and the other cleaved peptide product would have amino acids from the P1' of the ADMP-susceptible cleavage bond through the C-terminus. Thus, the reference teachings anticipate claims 15 and 16.

13. Claims 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Doege et al. (J

Biol Chem. 1991 Jan 15;266(2):894-902; and Accession A39086. 10-Sep-1999).

Doege et al. teach a peptide comprising amino acids 1-40 of SEQ ID NO: 1 (see enclosed alignment). Thus, the reference teaching anticipates claim 3 which is directed toward a peptide comprising amino acids 1-40 of SEQ ID NO: 1, and anticipates claim 4 which is directed toward a peptide comprising a sequence that is at least 80% identical to amino acids 1-40 of SEQ ID NO: 1.

14. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Hering et al. (Accession P13608. 01-JAN-1990).

Hering et al. teach a peptide comprising amino acids 1-40 of SEQ ID NO: 2 (see enclosed alignment). Thus, the reference teaching anticipates the claim 5 which is directed a peptide comprising 1-40 of SEQ ID NO: 2.

15. Claims 6 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Antonsson et al. (Accession A34234 20-March-1992).

Antonsson et al. teach a peptide comprising amino acids 1-40 of SEQ ID NO: 3 (see enclosed alignment). Thus, the reference teaching anticipates the claim 6 which is directed a peptide comprising 1-40 of SEQ ID NO: 3, and anticipates claim 7 which is directed toward a peptide comprising a sequence that is at least 80% identical to amino acids 1-40 of SEQ ID NO: 3.

Claim Rejections - 35 U.S.C. § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 2, 8, 9, 11-14, 17-21, 31, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fosang et al. (FEBS Lett. 1996 Feb 12;380(1-2):17-20) in view of Koritsas et al. (Anal Biochem. 1995; 227: 22-26).

The teachings of Fosang et al. have been stated above. Fosang et al. does not teach a biotinylated peptide substrate.

Koritsas et al. teach methods for attaching biotin to gelatin comprising contacting gelatin with biotinyl-N-hydroxysuccinimide ester, where the biotinylated gelatin is subsequently immobilized onto microtiter plates for use in a protease assay that is sensitive to all proteolytic classes tested (see entire publication, especially p.23, left column, section *Preparation of biotinylated Gelatin*)

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to biotinylate the aggrecan G1-G2 peptide substrate taught by Fosang et al. by contacting biotinyl-*N*-hydroxysuccinimide ester as taught by Koritsas et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to have a protease substrate that can be used in the protease assay taught by Koritsas et al., where the assay is sensitive to all proteolytic classes tested.

Since lysine residues are present in the N- and C-terminal of the peptide taught by Fosang et al., then they would be inherently biotinylated at these regions (see GenBank Accession NP_037359 and NP_001126).

Subjecting the aggrecan G1-G2 peptide to a specific ADMP would result in proteolytically cleaved peptides comprising amino acid from the N-terminus through P1 of the ADMP-susceptible cleavage bond and proteolytically cleaved peptides comprising amino acid from the P1' of the ADMP-susceptible cleavage bond through C-terminus. Since the biotinylated substrate would be cleaved by a specific ADMP, then the cleaved peptide fragments would by still be biotinylated at specific lysine residues. Furthermore, it is within the purview of one of skill in the art to esterify of replace the P1 amino acid Glu as recited in claims 31 and 32 in order to prevent proteolytic hydrolysis of the substrate peptide.

18. Claims 10, 22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fosang et al. in view of Koritsas et al. as applied to claims 2, 8, 9, 11-14, 17-21, 31, and 32 above, and further in view of Duan et al. (Anal Biochem. 1994 Feb 1;216(2):431-8).

Duan et al. teach method for adding the chromophore FTC (fluoresceinylthiocarbamyl) to peptides for use in assaying protease activity (see entire publication, especially pp. 431-433).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the chromophore FTC taught by Duan et al. to the aggrecan G1-G2 peptide substrate taught by Fosang et al.. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to have a protease substrate that can be used in the protease assay taught by Duan et al.

Conclusion

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

21. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

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